REMARKS

Claims 21-29 are pending in the application. Claims 21-29 have been rejected.

OBJECTION TO THE ABSTRACT UNDER 37 C. F. R. §1.72

In the Office Action, the Examiner objected to the abstract as allegedly not setting forth the salient characteristics of the claimed invention.

In response, in order to expedite prosecution, Applicants have herein amended the abstract.

Accordingly, Applicants respectfully request withdrawal of the objection.

CLAIM REJECTIONS

35 U.S.C. § 112 Rejections

In the Office Action, the Examiner rejected claims 21-29 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time of filing, had possession of the claimed invention. The Examiner alleged that the disclosure does not sufficiently describe the generation of other suitable Listeria auxotrophs and does not provide a reproducible means for obtaining the same.

Applicants respectfully disagree. Applicants assert that the subject specification provides clear written description of auxotrophic attenuated strains of Listeria, and is not limited to dal and dat strains, as the Examiner has alleged:

> "The invention includes a method of eliciting a T cell immune response to an antigen in a mammal comprising administering to

the mammal an auxotrophic attenuated strain of Listeria which expresses the antigen, wherein the auxotrophic attenuated strain comprises a mutation in at least one gene whose protein product is essential for growth of the Listeria" (paragraph 9; emphasis added).

As the Examiner has admitted, the subject specification describes D-alanine mutant Listeria strains attenuated in the dal and dat genes (paragraph 86). However, other auxotrophic mutants are described as well in the subject specification. For example, the subject specification discloses auxotrophic Listeria strains deficient in synthesis of D-glutamic acid (paragraph 0040). Further, the subject specification describes inactivation of the glutamate racemase gene, dga (paragraph 0040). Further, the subject specification describes auxotrophic Listeria strains deficient in genes involved in the synthesis of diamimopimelic acid (paragraph 0040). Further, the subject specification describes inactivation of a gene encoding aspartate beta-semialdehyde dehydrogenase (paragraph 0040).

Further, the subject specification describes auxotrophic Listeria strains deficient in additional genes involved in D-alanine synthesis (paragraph 0038). Further, the subject specification describes auxotrophic Listeria strains deficient in genes involved in synthesis of other metabolic components in a bacterial cell such as glutamate racemase gene, dga and a gene encoding aspartate beta-semialdehyde dehydrogenase (paragraph 0040).

Thus, the subject specification is not limited to dal and dat strains, as the Examiner has alleged, but rather describes additional auxotrophic strains of Listeria. Accordingly, the full scope of the invention recited in the subject claims is fully described in the subject specification.

Further, auxotrophic attenuated strains of Listeria and methods for generating the same were well known to a person of average skill in the art at the time of filing the subject application. For example, Camilli et al. (Camilli A, Portnoy A, and Youngman P. J. Bacteriol. 1990 Jul;172(7):3738-44, a copy of which is attached hereto)) isolated and mapped

auxotrophic *L. monocytogenes* strains that were obtained after mutagenesis, including auxotrophs for adenosine, uracil, proline, glycine, nicotinic acid, phenylalanine, glutamine, and aromatic amino acids (see table 2, p. 3741).

In addition, the Marquis et al. reference (Marquis H, Bouwer HG, Hinrichs DJ, and Portnoy DA. Infect Immun. 1993 Sep;61(9):3756-60. (a copy of which is attached hereto)) disclosed adenine, phenylalanine, tryptophan, tyrosine, glycine, proline, threonine, niacine, and uracil auxotrophic *L. monocytogenes* strains. Auxotrophic *L. monocytogenes* strains described by Marquis et al. were catalogued according to the inactivated gene that created the particular auxotroph (see table 1, p. 3757).

In addition, the Sleator et al. reference (Sleator RD, Gahan CG, and Hill C. Appl Environ Microbiol. 2001 Jun;67(6):2571-7 (a copy of which is attached hereto)) obtained and characterized *L. monocytogenes* proB, mutant, an auxotroph, in Proline-deficient medium (pp. 2573-2576).

Applicants respectfully assert that, in light of the teachings of the subject specification, a person of average skill in the art would have been able to substitute the attenuated auxotrophic strains known in the art, e.g. those described by Camilli et al., Marquis et al., and Sleator et al., for the attenuated auxotrophic strains described in the subject specification.

Accordingly, Applicants respectfully request withdrawal of the rejection.

Further, the Examiner rejected claims 21-29 as allegedly not being sufficiently enabled in a manner commensurate with their scope.

Applicants respectfully disagree. The subject specification clearly enables a person skilled in the art to construct and use a variety of *L. monocytogenes* auxotrophs. As the Examiner admitted, Applicants provided in the specification materials and methods useful in the construction and use of an attenuated auxotrophic dal/dat *L. monocytogenes* strain. Essentially, an auxotrophic strain of *L. monocytogenes* which requires D-alanine for growth is constructed as described in paragraph 92-97.

Additionally, the subject specification contains description that will enable one of skill in the art to generate D-glutamic acid auxotrophic mutants. In paragraph 0040 the specification provides that:

> "To generate D-glutamic acid auxotrophic mutants, it is necessary to inactivate the dat gene, which is involved in the conversion of D-glu+pyr to alpha-ketoglutarate+D-ala and the reverse reaction. It is also necessary to inactivate the glutamate racemase gene, dga" (emphasis added).

Thus, the subject specification enabled the generation of an additional attenuated auxotrophic *L. monocytogenes* strain, a D-glutamic acid auxotrophic mutant.

Further, the subject specification provided a diamimopimelic acid attenuated auxotrophic *L. monocytogenes* strain in which a gene encoding aspartate beta-semialdehyde dehydrogenase is inactivated as described in Sizemore et al., 1995 (paragraph 0040).

Thus, the subject specification specifically enabled the generation of a representative number of attenuated auxotrophic *L. monocytogenes* strains. Accordingly, the full scope of the invention recited in the subject claims is fully enabled in the subject specification.

Applicants assert that it would have been clear to a person of average skill in the art that the experimental methods described in the Examples of the subject specification are applicable to the other auxotrophic Listeria strains disclosed therein, such as auxotrophic strains of Listeria comprising genes involved in the synthesis of the cell wall as described in the subject specification (paragraph 0040).

Further, based on the state of the art at time of filing of the present Application, additional methods for obtaining mutant, auxotrophic strains of Listeria were well known in the art. Camilli et al. obtained representative species of auxotrophic stains of Listeria such as adenosine, uracil, proline, glycine, nicotinic acid, phenylalanine, glutamine, and aromatic amino acids auxotrophs, based on transposon-mediated insertional mutagenesis via the introduction of the conjugative transposons Tn*JS45* and Tn*9J6* (pp.3738-3740). Thus, based

on Camilli et al., a person of average skill in the art would clearly know how to generate and test the strains described hereinabove.

Further, Marquis et al. used auxotrophic *L. monocytogenes* strains after mutagenesis with Tn917-LTV3 to obtain representative species of auxotrophic stains of Listeria such as adenine, phenylalanine, tryptophan, tyrosine, glycine, proline, threonine, niacine, and uracil auxotrophs (p. 3757). Thus based on Marquis et al. a person of average skill in the art would clearly know how to generate and test the strains described hereinabove.

Further, Sleator et al. carried out an allelic exchange mutagenesis to create a 1,394-bp deletion in the proBA operon. The resulting mutant, designated PSOE, exhibited complete proline auxotrophy.(p.2574). Thus based on Sleator et al. a person of average skill in the art would clearly know how to generate and test the strains described hereinabove.

Hence, the present invention enables a person of skill in the art to make and use *L. monocytogenes* auxotrophs, in view of what was known in the art at the time of filing the subject application.

Accordingly, Applicants respectfully request withdrawal of the rejection.

In view of the foregoing remarks, the pending claims are deemed to be allowable. Their favorable reconsideration and allowance is respectfully requested.

Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below. Similarly, if there are any further issues yet to be resolved to advance the prosecution of this application to issue, the Examiner is requested to telephone the undersigned counsel.

Please charge any fees associated with this paper to deposit account No. 50-3355.

Respectfully submitted,

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